REMARKS

Applicants have amended the abstract so as not to include the title "Sustained Release Drug Composition." The Examiner required this correction.

Claims 1-46 are pending in the application. Cl[redacted]12-25 are drawn to an elected invention. Among them, claim 12 is the only independe[redacted]aim.

Reconsideration of the application is request[redacted]iew of the following remarks.

Rejections Under 35 U.S.C. 103(a)

Claims 12-25 are directed toward a method for producing a sustained release drug composition. The Examiner has rejected claims 12-25 under 35 U.S.C. 103(a) as being unpatentable over Suzuki et al. EP 0 913149 A1 (Suzuki) in view of Igari et al. US 5,344,644 (Igari). Applicants respectfully traverse.

Independent claim 12 recites the following steps: "providing a precipitating solution containing a mucopolysaccharide, the carrier protein, and a drug; lowering the pH of the precipitating solution to a level sufficient to form an insoluble product comprising the mucopolysaccharide, the carrier protein, and the drug; and collecting from the precipitating solution the insoluble product (emphasis added; page 13 of the application, lines 3-7). " Applicants concur with the Examiner that Suzuki discloses preparative steps that are operationally comparable to the "providing" and "collecting" steps recited in claim 12. However, as discussed immediately below, neither Suzuki nor Igari teaches the "lowering the pH" step, so it the Applicants' position that the combination of the two references fails to teach all elements of the claimed method.

According to the Examiner:

> "Suzuki does not explicitly disclose lowering the pH of the precipitating solution; however, one of ordinary skill in the art would recognize that the addition of an acidic solution would indeed lower the pH of the solution" (Office Action, page 5, lines 3-5).

Applicants acknowledge that very dilute acetic acid solutions (e.g., 1%) are used in the Suzuki preparations. However, these solutions are used merely to solubilize certain 'ingredient (a)' macromolecules (page 4, lines 26-28). To the extent that Suzuki discloses using acid to

solubilize certain components of a composition, it teaches away from the use of acid to precipitate a product. In any event, no mention or suggestion is made in Suzuki that the use of acidic solutions promotes or facilitates precipitation of the desired drug compositions in any way. Further, although all drug compositions in Suzuki are ultimately obtained by precipitation, none of them are precipitated by acetic acid. The compositions precipitate because they are insoluble in the aqueous preparatory solutions. Thus, it would not have been an obvious improvement or modification over the Suzuki method to incorporate a pH-lowering step into a sustained release drug preparation method.

Applicants also disagree with the Examiner's statement on the other reference: "Igari teaches that the lowering the pH of a composition below 4 will cause the formation of a precipitate" (Office Action, page 5, lines 18-20). This statement was followed by a reference to this passage from Igari:

> "The pH of a solution prepared from the water-soluble composition of the present invention should be such that said pH will not exert any adverse influence upon the activity of the pharmacologically active peptide but is within an acceptable range for injections in general and further such that said pH will neither cause a great change in viscosity nor allow formation of a precipitate or the like. Thus the solution should preferably have a pH of about 4 to 8, more preferably about 5 to 8" (Igari, column 6, lines 43-51).

The "lowering the pH" step in claim 12 specifically effects precipitation of the drug composition, which is isolated as a solid from the supernatant liquid prior to administration to a subject. The drug compositions obtained by this method are pharmacologically active (Specification, pages 10-11, Example 10). The above-quoted Igari passage merely describes pH parameters for maintaining pharmacologically active, non-viscous and homogeneous solutions of the drug compositions. In other words, in Igari, there is no precipitation and isolation of the compositions prior to administration to the subject. Further, Igari does not teach or suggest in any way that acidifying a solution of the drug composition will result in precipitation of pharmacologically active, sustained release drug compositions in solid form.

Igari actually teaches away from low pH conditions. Below is another passage from Igari:

> "[T]he viscosity of hyaluronic acid can be increased by reducing the pH into the acid side (e.g. to about 2.5). However, a higher hyaluronic acid

viscosity means a greater difficulty in administering an injection. (Igari, column 2, lines 22-26)."

Igari teaches that low pH correlates with increased solution viscosity and that the acidified solutions are more difficult to handle because of their reduced fluidity. Thus, Igari specifically teaches away from working at low pH.

For the reasons set forth above, both Suzuki and Igari teach away or at least do not suggest lowering the pH to facilitate precipitation of a drug composition, as required by claim 12. In other words, claim 12 is not rendered obvious by Suzuki and Igari. Since claims 13-25 depend from claim 12, they are also not rendered obvious by these two references.

To complete the record, Applicants address two additional grounds for obviousness raised by the Examiner: (1) "it would have also been obvious to one of ordinary skill in the art to use γ-globulin" (Office Action, page 6, lines 5-6); and (2) "it would have been obvious to the skilled artisan that composition as disclosed by Suzuki may also be in lyophilized form" (Office Action, page 6, lines 9-11). The use of γ-globulin as a carrier protein and the step of lyophilizing are respectively limitations of claims 17 and 25. These claims do not have to rely on these two limitations for patentability. They depend from claim 12 and are not rendered obvious by Suzuki and Igari for the reasons set forth above.

Attached is a marked-up version of the changes being made by the current amendment.

Applicant asks that all claims be allowed. Please apply any charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

Date: 10-25-02

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Version with markings to show changes made

In the abstract:

-- [SUSTAINED RELEASE DRUG COMPOSITIONS]

Abstract of the Disclosure

The invention relates to a composition providing sustained release of a drug, the composition including (1) a mucopolysaccharide, a carrier protein, and a drug; or (2) a mucopolysaccharide and a protein drug. --